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FORM PTO-1390 (Modified) (REV 10-2000) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

ATTORNEY'S DOCKET NUMBER	
NIDN-10403	

U S APPLICATION NO (IF KNOWN, SEE 37 CFR)	INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
To be assigned 10/018026	PCT/GB00/01960	May 22, 2000	May 21, 1999

TITLE OF INVENTION

Method of Magnetic Resonance Imaging

APPLICANT(S) FOR DO/EO/US

Atle Bjornerud, Karen Briley-Saebo, Michael V. Knopp, Stephen McGill, and Stefan O. Schoenberg

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☒ This is an express request to begin national examination procedures (35 U.S.C. 371(f)). The submission must include itens (5), (6), (9) and (24) indicated below.
4. ☒ The US has been elected by the expiration of 19 months from the priority date (Article 31).
5. ☒ A copy of the International Application as filed (35 U.S.C. 371 (c) (2))
   a. ☒ is attached hereto (required only if not communicated by the International Bureau).
   b. ☒ has been communicated by the International Bureau.
   c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ☐ An English language translation of the International Application as filed (35 U.S.C. 371(c)(2)).
   a. ☐ is attached hereto.
   b. ☐ has been previously submitted under 35 U.S.C. 154(d)(4).
7. ☐ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371 (c)(3))
   a. ☐ are attached hereto (required only if not communicated by the International Bureau).
   b. ☐ have been communicated by the International Bureau.
   c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
   d. ☐ have not been made and will not be made.
8. ☐ An English language translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
9. ☒ An oath or declaration of the inventor(s) (35 U.S.C. 371 (c)(4)).
10. ☐ An English language translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371 (c)(5)).
11. ☒ A copy of the International Preliminary Examination Report (PCT/IPEA/409).
12. ☒ A copy of the International Search Report (PCT/ISA/210).

Items 13 to 20 below concern document(s) or information included:

13. ☒ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
14. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
15. ☐ A **FIRST** preliminary amendment.
16. ☐ A **SECOND** or **SUBSEQUENT** preliminary amendment.
17. ☐ A substitute specification.
18. ☐ A change of power of attorney and/or address letter.
19. ☐ A computer-readable form of the sequence listing in accordance with PCT Rule 13ter.2 and 35 U.S.C. 1.821 - 1 825.
20. ☐ A second copy of the published international application under 35 U.S.C. 154(d)(4).
21. ☐ A second copy of the English language translation of the international application under 35 U.S.C. 154(d)(4).
22. ☒ Certificate of Mailing by Express Mail
23. ☒ Other items or information:

copy of this transmittal letter for charging purposes
return postcard

APPLICATION NO (IF KNOWN, SEE 37 CFR)	INTERNATIONAL APPLICATION NO	ATTORNEY'S DOCKET NUMBER
To be assigned 10/018026	PCT/GB00/01960	NIDN-10403

4. The following fees are submitted:.

BASIC NATIONAL FEE (37 CFR 1.492 (a) (1) - (5)) :		CALCULATIONS PTO USE ONLY
☐ Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO	$1040.00	
☒ International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO	$890.00	
☐ International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO	$740.00	
☐ International preliminary examination fee (37 CFR 1.482) paid to USPTO but all claims did not satisfy provisions of PCT Article 33(1)-(4)	$710.00	
☐ International preliminary examination fee (37 CFR 1.482) paid to USPTO and all claims satisfied provisions of PCT Article 33(1)-(4)	$100.00	
ENTER APPROPRIATE BASIC FEE AMOUNT =		$890.00
Surcharge of **$130.00** for furnishing the oath or declaration later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492 (e)).		$0.00

CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE	
Total claims	23 - 20 =	3	x $18.00	$54.00
Independent claims	2 - 3 =	0	x $84.00	$0.00
Multiple Dependent Claims **(check if applicable)**.			☐	$0.00
TOTAL OF ABOVE CALCULATIONS =				$944.00
☐ Applicant claims small entity status. See 37 CFR 1.27). The fees indicated above are reduced by 1/2.				$0.00
SUBTOTAL =				$944.00
Processing fee of **$130.00** for furnishing the English translation later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492 (f)). +				$0.00
TOTAL NATIONAL FEE =				$944.00
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31) **(check if applicable).** ☐				$0.00
TOTAL FEES ENCLOSED =				$944.00
			Amount to be: refunded	$
			charged	$

a. ☐ A check in the amount of _____ to cover the above fees is enclosed.

b. ☒ Please charge my Deposit Account No. **500-588** in the amount of **$944.00** to cover the above fees. A duplicate copy of this sheet is enclosed.

c. ☒ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. **500-588** A duplicate copy of this sheet is enclosed.

d. ☐ Fees are to be charged to a credit card. **WARNING:** Information on this form may become public. **Credit card information should not be included on this form.** Provide credit card information and authorization on PTO-2038.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO:

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SIGNATURE

Royal N. Ronning, Jr.
NAME

32,529
REGISTRATION NUMBER

October 29, 2001
DATE

NIDN-10403

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of:	A. Bjornerud, et al.	Group Art Unit:	To be assigned
Serial Number:	To be assigned	Examiner:	To be assigned
Filing Date:	October 29, 2001		
Title:	Method of Magnetic Resonance Imaging		

FIRST PRELIMINARY AMENDMENT

Honorable Assistant Commissioner of Patents
Box Patent Application
Washington, D.C. 20231

Sir:

Please consider the following amendments and remarks in connection with the prosecution of the captioned application, which is a filing under 35 U.S.C. § 371 and claims priority to international application number PCT/GB00/01960 filed May 22, 2000. This application also claims priority to patent applications filed in Great Britain assigned number 9911939.8 filed May 21, 1999 and 0007867.5 filed March 31, 2000.

In the Claims

Please amend page 21, line 1, as follows:

[Claims]

What is claimed is:

Please cancel claim 13, without prejudice.

Please amend claim 1 as follows:

1. (once amended) A method of magnetic resonance imaging of [the]a kidney in a [vascularised]human or non human body having a vasculature comprising administering [wherein]a blood pool MR contrast agent [is administered]into the vasculature of said body and generating one or more images of said kidney[are generated] using imaging sequences and timing to permit both visualisation and gradation of renal artery stenosis and quantification of renal perfusion[, and, optionally, values indicative of renal artery stenosis grade and renal perfusion are generated from said images or from detected magnetic resonance signals capable of transformation into said angiograms].

Please amend claim 2 as follows:

2. (once amended) A method of differentiation between renovascular damage and renoparenchymal damage in a kidney in a [vascularised]human or non human body having a vasculature comprising administering [wherein]a blood pool MR contrast agent [is administered]into the vasculature of said body and generating one or more images of said kidney [are generated]using imaging sequences and timing to permit both visualisation and gradation of renal artery stenosis and quantification of renal perfusion, and wherein [the]a physiological and morphological state of said kidney is assessed.

Please amend claim 3 as follows:

3. (once amended) [A]The method [as claimed in claim 1 or claim 2]of claim 1 wherein said blood pool MR contrast agent is superparamagnetic contrast agent.

Please amend claim 4 as follows:

4. (once amended) [A]The method [as claimed in any of claims 1 to 3]of claim 1 wherein said blood pool MR contrast agent comprises magnetic iron oxide particles having on their surfaces an optionally modified polysaccharide and optionally a material which inhibits opsonization.

Please amend claim 5 as follows:

5. (once amended) [A]The method [as claimed in any of claims 1 to 4]of claim 1 wherein said blood pool MR contrast agent comprises superparamagnetic iron oxide particles having on their surfaces degraded starch[and optionally a functionalised PEG].

Please amend claim 6 as follows:

6. (once amended) [A]The method [as claimed in any of claims 1 to 5]of claim 1 wherein said blood pool MR contrast agent is administered as a bolus.

Please amend claim 7 as follows:

7. (once amended) [A]The method of claim 6 wherein a contrast enhanced image of said kidney is generated during the first pass of said contrast agent.

Please amend claim 8 as follows:

8. (once amended) [A]The method of claim 7 wherein said image is a T_2*-weighted image.

Please amend claim 9 as follows:

9. (once amended) [A]The method of [any of claims 6 to 8]claim 6 wherein at least one further image of said kidney is generated after the concentration of said contrast agent throughout the blood of said body has become substantially uniform.

Please amend claim 10 as follows:

10. (once amended) [A]The method of claim 9 wherein at least one T_1-weighted image is generated after the concentration of said contrast agent throughout the blood of said body has become substantially uniform.

Please amend claim 11 as follows:

11. (once amended) [A]The method of claim 9[or claim 10] comprising at least one further administration of said contrast agent.

Please amend claim 12 as follows:

12. (once amended) [A]The method of [any of claims 1 to 11]claim 14 wherein values indicative of renal perfusion and renal artery stenosis grade are derived from said MR images.

Please add new claim 14 as follows:

14. (new) The method of claim 1, further comprising generating values of renal perfusion and renal artery stenosis from said images or detected magnetic resonance signal capable of transformation into angiograms.

Please add new claim 15 as follows:

15. (new) The method of claim 2 wherein said blood pool MR contrast agent is superparamagnetic contrast agent.

Please add new claim 16 as follows:

16. (new) The method of claim 2 wherein said blood pool MR contrast agent comprises magnetic iron oxide particles having on their surfaces an optionally modified polysaccharide and optionally a material which inhibits opsonization.

Please add new claim 17 as follows:

17. (new) The method of claim 2 wherein said blood pool MR contrast agent comprises superparamagnetic iron oxide particles having on their surfaces degraded starch.

Please add new claim 18 as follows:

18. (new) The method of claim 2 wherein said blood pool MR contrast agent is administered as a bolus.

Please add new claim 19 as follows:

19. (new) The method of claim 18 wherein a contrast enhanced image of said kidney is generated during the first pass of said contrast agent.

Please add new claim 20 as follows:

20. (new) The method of claim 19 wherein said image is a T_2*-weighted image.

Please add new claim 21 as follows:

21. (new) The method of claim 18 wherein at least one further image of said kidney is generated after the concentration of said contrast agent throughout the blood of said body has become substantially uniform.

Please add new claim 22 as follows:

22. (new) The method of claim 21 wherein at least one T_1-weighted image is generated after the concentration of said contrast agent throughout the blood of said body has become substantially uniform.

Please add new claim 23 as follows:

23. (new) The method of claim 21 comprising at least one further administration of said contrast agent.

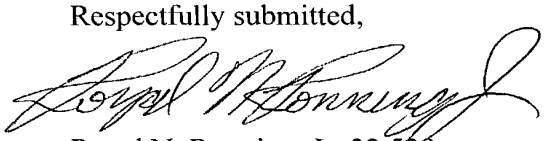
Remarks

Claims 1-13 are pending in the instant application. Applicants have amended claims 1-12 to more fully conform with U.S. practice and to delete multiple dependencies. Applicants have cancelled claim 13, without prejudice. Applicants have added new claims 14-23. A version of the claims marked up to show the amendments, as well as a clean version of the claims encompassing the amendments, is attached hereto.

Applicants respectfully assert that all amendments are fairly based on the specification, and respectfully request their entry.

Applicants believe that the claims, as amended, are in allowable form, and earnestly solicit the allowance of claims 1-12 and 14-23.

Respectfully submitted,



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Claims (marked-up version showing amendment(s))

Page 21, line 1:

[Claims]

What is claimed is:

1. (once amended) A method of magnetic resonance imaging of [the]a kidney in a [vascularised]human or non human body having a vasculature comprising administering [wherein]a blood pool MR contrast agent [is administered]into the vasculature of said body and generating one or more images of said kidney[are generated] using imaging sequences and timing to permit both visualisation and gradation of renal artery stenosis and quantification of renal perfusion[, and, optionally, values indicative of renal artery stenosis grade and renal perfusion are generated from said images or from detected magnetic resonance signals capable of transformation into said angiograms].

2. (once amended) A method of differentiation between renovascular damage and renoparenchymal damage in a kidney in a [vascularised]human or non human body having a vasculature comprising administering [wherein]a blood pool MR contrast agent [is administered]into the vasculature of said body and generating one or more images of said kidney [are generated]using imaging sequences and timing to permit both visualisation and gradation of renal artery stenosis and quantification of renal perfusion, and wherein [the]a physiological and morphological state of said kidney is assessed.

3. (once amended) [A]The method [as claimed in claim 1 or claim 2]of claim 1 wherein said blood pool MR contrast agent is superparamagnetic contrast agent.

4. (once amended) [A]The method [as claimed in any of claims 1 to 3]of claim 1 wherein said blood pool MR contrast agent comprises magnetic iron oxide particles having on their surfaces an optionally modified polysaccharide and optionally a material which inhibits opsonization.

5. (once amended) [A]The method [as claimed in any of claims 1 to 4]of claim 1 wherein said blood pool MR contrast agent comprises superparamagnetic iron oxide particles having on their surfaces degraded starch[and optionally a functionalised PEG].

6. (once amended) [A]The method [as claimed in any of claims 1 to 5]of claim 1 wherein said blood pool MR contrast agent is administered as a bolus.

7. (once amended) [A]The method of claim 6 wherein a contrast enhanced image of said kidney is generated during the first pass of said contrast agent.

8. (once amended) [A]The method of claim 7 wherein said image is a T_2*-weighted image.

[redacted]

9. (once amended) [A]The method of [any of claims 6 to 8]claim 6 wherein at least one further image of said kidney is generated after the concentration of said contrast agent throughout the blood of said body has become substantially uniform.

10. (once amended) [A]The method of claim 9 wherein at least one T_1-weighted image is generated after the concentration of said contrast agent throughout the blood of said body has become substantially uniform.

11. (once amended) [A]The method of claim 9[or claim 10] comprising at least one further administration of said contrast agent.

12. (once amended) [A]The method of [any of claims 1 to 11]claim 14 wherein values indicative of renal perfusion and renal artery stenosis grade are derived from said MR images.

14. (new) The method of claim 1, further comprising generating values of renal perfusion and renal artery stenosis from said images or detected magnetic resonance signal capable of transformation into angiograms.

15. (new) The method of claim 2 wherein said blood pool MR contrast agent is superparamagnetic contrast agent.

16. (new) The method of claim 2 wherein said blood pool MR contrast agent comprises magnetic iron oxide particles having on their surfaces an optionally modified polysaccharide and optionally a material which inhibits opsonization.

17. (new) The method of claim 2 wherein said blood pool MR contrast agent comprises superparamagnetic iron oxide particles having on their surfaces degraded starch.

18. (new) The method of claim 2 wherein said blood pool MR contrast agent is administered as a bolus.

19. (new) The method of claim 18 wherein a contrast enhanced image of said kidney is generated during the first pass of said contrast agent.

20. (new) The method of claim 19 wherein said image is a T_2*-weighted image.

21. (new) The method of claim 18 wherein at least one further image of said kidney is generated after the concentration of said contrast agent throughout the blood of said body has become substantially uniform.

22. (new) The method of claim 21 wherein at least one T_1-weighted image is generated after the concentration of said contrast agent throughout the blood of said body has become substantially uniform.

23. (new) The method of claim 21 comprising at least one further administration of said contrast agent.

Claims (clean version encompassing amendments)

What is claimed is:

1. (once amended) A method of magnetic resonance imaging of a kidney in a human or non human body having a vasculature comprising administering a blood pool MR contrast agent into the vasculature of said body and generating one or more images of said kidney using imaging sequences and timing to permit both visualisation and gradation of renal artery stenosis and quantification of renal perfusion.

2. (once amended) A method of differentiation between renovascular damage and renoparenchymal damage in a kidney in a human or non human body having a vasculature comprising administering a blood pool MR contrast agent into the vasculature of said body and generating one or more images of said kidney using imaging sequences and timing to permit both visualisation and gradation of renal artery stenosis and quantification of renal perfusion, and wherein a physiological and morphological state of said kidney is assessed.

3. (once amended) The method of claim 1 wherein said blood pool MR contrast agent is superparamagnetic contrast agent.

4. (once amended) The method of claim 1 wherein said blood pool MR contrast agent comprises magnetic iron oxide particles having on their surfaces an optionally modified polysaccharide and optionally a material which inhibits opsonization.

5. (once amended) The method of claim 1 wherein said blood pool MR contrast agent comprises superparamagnetic iron oxide particles having on their surfaces degraded starch.

6. (once amended) The method of claim 1 wherein said blood pool MR contrast agent is administered as a bolus.

7. (once amended) The method of claim 6 wherein a contrast enhanced image of said kidney is generated during the first pass of said contrast agent.

8. (once amended) The method of claim 7 wherein said image is a T_2*-weighted image.

9. (once amended) The method of claim 6 wherein at least one further image of said kidney is generated after the concentration of said contrast agent throughout the blood of said body has become substantially uniform.

10. (once amended) The method of claim 9 wherein at least one T_1-weighted image is generated after the concentration of said contrast agent throughout the blood of said body has become substantially uniform.

11. (once amended) The method of claim 9 comprising at least one further administration of said contrast agent.

12. (once amended) The method of claim 14 wherein values indicative of renal perfusion and renal artery stenosis grade are derived from said MR images.

14. (new) The method of claim 1, further comprising generating values of renal perfusion and renal artery stenosis from said images or detected magnetic resonance signal capable of transformation into angiograms.

15. (new) The method of claim 2 wherein said blood pool MR contrast agent is superparamagnetic contrast agent.

16. (new) The method of claim 2 wherein said blood pool MR contrast agent comprises magnetic iron oxide particles having on their surfaces an optionally modified polysaccharide and optionally a material which inhibits opsonization.

17. (new) The method of claim 2 wherein said blood pool MR contrast agent comprises superparamagnetic iron oxide particles having on their surfaces degraded starch.

18. (new) The method of claim 2 wherein said blood pool MR contrast agent is administered as a bolus.

19. (new) The method of claim 18 wherein a contrast enhanced image of said kidney is generated during the first pass of said contrast agent.

20. (new) The method of claim 19 wherein said image is a T_2*-weighted image.

21. (new) The method of claim 18 wherein at least one further image of said kidney is generated after the concentration of said contrast agent throughout the blood of said body has become substantially uniform.

22. (new) The method of claim 21 wherein at least one T_1-weighted image is generated after the concentration of said contrast agent throughout the blood of said body has become substantially uniform.

23. (new) The method of claim 21 comprising at least one further administration of said contrast agent.

Method of Magnetic Resonance Imaging

The present invention relates to improvements in and relating to methods of magnetic resonance imaging (MRI) of the kidneys.

Renal artery stenosis, the narrowing of the artery supplying blood to the kidney, can cause two effects - hypertension and renal insufficiency. Hypertension can result in large vessel disease and complications such as myocardial infarction and central nervous system bleeding. Renal insufficiency potentially leads to end stage renal failure resulting in the necessity for life-long dialysis and the risk of death. While renal artery stenosis is a relatively rare cause of hypertension affecting only 0.5 to 5% of the general population (see: Lewin et al., Arch. Intern. Med. 145: 424-427 (1985); Ying et al., N. Engl. J. Med. 311: 1070-1075 (1984); Swales, Lancet I: 577-579 (1976); and Arch. Intern. Med. 147: 820-829 (1987)), it has a high incidence in patients with pre-existing vascular disease. Moreover, in patients with diabetes the incidence rises to 10%, in patients with abdominal aortic aneurysms the incidence rises to over 20%, and in patients with peripheral vascular disease the incidence rises to over 40% (see: Sawicki et al., J. Intern. Med. 229: 489-492 (1991); and Missouris et al., Am. J. Med. 96: 10-14 (1994)).

Assessment of renal artery stenosis however is problematic for several reasons. Firstly, reliable detection and gradation of severity of the stenosis is required and in order to screen a large population of patients the procedure used must be safe, cost effective and accurate. Secondly, if the presence of a renal artery stenosis is detected, it is important to determine whether this is actually related to the patient's hypertension or renal insufficiency since only 10% of renal disease is due to renovascular

abnormalities with the rest generally being caused by diseases of the renal parenchyma, e.g. inflammatory diseases such as glomerulonephritis. Nonetheless chronic ischemia arising from renal artery stenosis can cause pathological changes to the renal parenchyma. Thirdly, since renoparenchymal and renovascular diseases can co-exist, it is important to determine the extent to which a renal artery stenosis is contributing to the overall malfunctioning of the kidney, i.e. to determine the hemodynamic and functional significance of the stenosis. Fourthly and most importantly, it is important to determine whether the benefit to the patient's renal function from removal of a renal artery stenosis will outweigh the risks of intervention. Moreover, there is only limited capacity for surgical revascularisation of patients with renal artery stenosis and the enormous costs of dialysis and organ transplant could be significantly reduced if the most appropriate candidates for surgical revascularisation can be selected.

Until now, the "gold standard" for diagnosis of renal artery stenosis has been X-ray digital subtraction angiography (DSA). However this technique is invasive since it involves catheterisation of the aorta and exposure of the patient to ionizing radiation and to renally excreted (and hence potentially nephrotoxic) contrast media. The problem of nephrotoxicity is particularly worrying since most patients investigated already suffer from some degree of renal insufficiency. Due to these drawbacks DSA is not considered particularly useful as a general screening technique. Furthermore, DSA is not able to quantify the extent of parenchymal damage and so is limited in its ability to be used in predicting the overall outcome of renal revascularisation. Other techniques for diagnosis of renal artery stenosis exist which involve ultrasound or renal scintigraphy and are non-invasive. However while

such techniques allow an assessment of renal function they do not permit accurate assessment of vascular morphology. Nonetheless, scintigraphy is currently considered to be the gold standard for measurement of renal perfusion and excretory function.

MRI has the great attractions of being non-invasive and allowing combination of multiple imaging strategies permitting both functional and morphological evaluation of the organ or tissue under investigation. While initially the emphasis in MRI was on imaging areas of the body without motion (e.g. the brain) and abdominal MRI, e.g. renal MR angiography, was subject to artefacts and not widely used, within recent years faster imaging procedures allowing image acquisition in less than a second have been developed and the area of MRI application has expanded into the chest and abdomen.

The introduction of contrast enhanced 3D MR angiography in a single breath-hold has allowed high quality angiography to be performed without the serious potential for nephrotoxicity (see: Prince et al., Radiology 197: 785-792 (1995)). The sensitivity and specificity of the technique for detection of a renal artery stenosis are now consistently reported as being about 95% (see: Hany et al., Radiology 204: 357-362 (1997); Snidow et al., Radiology 198: 725-732 (1996); Steffens et al., JMRI 7: 617-622 (1997); Bakker et al., Radiology 207: 497-504 (1998); and Wilman et al., Radiology 205: 137-146 (1997)).

This MRI technique however still suffers from various drawbacks. Firstly it is still relatively complex since, using the injectable MRI contrast agents currently commercially available (e.g. Magnevist, Omniscan or ProHance), image acquisition must be timed to coincide with the first passage of the agent through the renal arteries (for example using the technique of EP-B-656762 (Prince)) as these agents rapidly extravasate. Although a variety of techniques for

automatic or semi-automatic detection of contrast agent arrival have been developed (see for example Schoenberg et al., Invest Radiol. 33: 506-514 (1998)), image acquisition timing is still a complex issue.

Secondly, the spatial resolution achievable with first pass 3D MR angiography is three to five-fold lower than that of DSA. First pass imaging requires maximum coverage of the vessels of interest in a single breath-hold and thus wastes spatial resolution.

Thirdly, MR imaging using extracellular (ECF) contrast agents, such as the soluble gadolinium monochelates that are currently commercially available, cannot absolutely quantify the amount of parenchymal damage to the kidney since the kidney does not have a blood tissue barrier and the ECF agents immediately extravasate when passing through the glomeruli. Accordingly quantification of blood volume and blood flow is not feasible.

There is thus a need for an improved method of MRI which can be used to assess both renal function and morphology.

We have now found that quantification of both the morphological degree of renal artery stenosis and the renal parenchymal perfusion can be achieved in a single MR examination if a blood pool contrast agent, i.e. a contrast agent which remains in the intravascular space during the time course of the examination is used.

Viewed from one aspect the present invention thus provides a method of magnetic resonance imaging of the kidney in a vascularised human or non human (e.g. mammalian, avian or reptilian) body wherein a blood pool MR contrast agent is administered into the vasculature of said body and images of said kidney are generated using imaging sequences and timing to permit both visualisation and gradation of renal artery stenosis and quantification of renal perfusion, and, optionally, values indicative of renal artery stenosis grade and

renal perfusion are generated from said images or from detected magnetic resonance signals capable of transformation into said angiograms.

By a blood pool MR contrast agent is meant a magnetic (e.g. paramagnetic, ferromagnetic, ferrimagnetic or superparamagnetic) material capable of reducing the T_1 and/or T_2* of water protons and which if administered into the vascular space does not significantly leak out into the interstitium during the time course of the interventional or interoperative procedure, i.e. it is essentially confined to the vascular space until excreted or metabolized. Examples of such blood pool agents include polymeric chelates (e.g. cascade polymers or dendrimers carrying metallated chelate groups) and particulates, in particular iron oxides and liposomes. Generally the agent should have a blood half life of at least 5 minutes, preferably at least 30 minutes. By way of contrast, the first parenteral MR contrast agents Gd DTPA (Magnevist® from Schering), Gd DTPA-bismethylamide (Omniscan® from Nycomed Amersham) and Gd HP-D03A (ProHance®) are all extracellular fluid MR agents; they are water-soluble mono-chelates which following administration into the vasculature rapidly extravasate into the interstitium.

Blood pool agents of particular use in the method of this invention include low molecular weight chelates which bind to blood proteins, e.g. blood proteins such as albumin, for example DTPA or DOTA derivatised with protein binding groups, e.g. lipophilic side chains such as aromatic moieties, e.g. one or more phenyl ring systems. One such example is MS-325/Angiomark of EPIX.

Suitable polymer based contrast agents for use in the method of the present invention can be carbohydrate or protein based, e.g. CMD-DTPA-Gd of Guerbet (Carboxymethyl dextran-GdDTPA conjugates), GdDTPA polylysine conjugates, or cascade or dendrimer polymers, e.g. Gadomer 17 of Schering AG or similar cascade

polymers as described in US-A-5874061 (of Schering AG), herein incorporated by reference.

Suitable iron oxide (or doped iron oxide) based contrast agents for use in the method of the present invention are known in the field under the name of SPIO (superparamagnetic iron oxides) or USPIO (ultrasmall superparamagnetic iron oxides). Examples include carbohydrate stabilised iron oxide particles, e.g. dextran-stabilised particles such as Combidex of Advanced Magnetics, and NC100150 (Clariscan, Nycomed Amersham).

More particularly the magnetic iron oxide contrast agent is preferably a water-dispersible material comprising magnetic iron oxide particles having on their surfaces (e.g. as a coating), an optionally modified carbohydrate or polysaccharide or derivative thereof, e.g. a glucose unit containing optionally modified polysaccharide or derivative thereof, preferably an optionally modified dextran or starch or derivative thereof, for example a cleaved (e.g. oxidatively cleaved) starch or carboxylated dextran. Such iron oxide complexes preferably also comprise a further material (e.g. coating material), especially one which inhibits opsonization, e.g. a hydrophilic polymer, preferably a functionalized polyalkylene oxide, more preferably a functionalized polyethylene glycol (PEG), in particular methoxy PEG phosphate (MPP).

The iron oxide complexes preferably have a core (i.e. iron oxide particle) diameter (mode diameter) of 1 to 15 nm, more preferably 2-10 nm, especially 3-7 nm, a total diameter (mode particle size) of 1 to 100 nm, more preferably 5-50 nm, especially preferably 10-25 nm, an r_2/r_1 ratio at 0.47T and 40°C of less than 3, more preferably less than 2.3, still more preferably less than 2.0, especially preferably less than 1.8. The saturation magnetization (Msat) at 1T is preferably 10 to 100 emu/gFe, more preferably 30-90 emu/gFe.

Other particulate based systems of use in the method of the present invention include liposomal or emulsion based agents.

Furthermore, compound 7228 of Advanced Magnetics can be used in the method of the present invention, as can the materials described in WO 91/12025, WO 90/01899, WO 88/00060, WO 91/12526 and WO 95/05669, all to Advanced Magnetics, and those described in WO92/11037 and WO90/01295, all of which publications are incorporated herein by reference.

Viewed from a further aspect the present invention provides the use of a blood pool MR contrast agent for the manufacture of a contrast medium for use in a method of diagnosis comprising a method of imaging according to the invention.

The comprehensive morphological and functional approach to kidney imaging according to the invention can be used to guide the therapeutic strategies for patients with renal artery stenosis by establishing guidelines for revascularisation since the quantitative data generated by the method of the invention can be correlated with each other to differentiate between renovascular and renoparenchymal damage.

The blood pool contrast agent is desirably administered as a bolus, e.g. by injection or infusion into the vasculature over a short time period, preferably 1 minute or less, more preferably 5 seconds or less, most preferably 1 second or less. The bolus may be sharpened by using a saline injection chaser. Injection or infusion is preferably into a vein upstream of the kidney. Particularly preferably injection is at a site whereby bolus arrival at the kidney will occur within 60 seconds, preferably 10 to 25 seconds. If a particularly sharp bolus is desired, injection may be into the renal artery itself.

In order to quantitate tissue perfusion (in terms of organ perfusion) in units of ml blood/min/g tissue)

the transient effect of the contrast agent in the tissue must be observed. This is best achieved by measuring the first pass effect of the agent in the tissue after a bolus injection of the agent.

The dosage of the contrast agent used according to the invention will depend upon the species, the longitudinal relaxivity of the agent, the magnetic moment of the agent at the imaging field strength and the sequence parameters used to acquire the image.

Concentration of a blood pool contrast agent is typically 0.01 - 10 mM in blood during examination.

The blood pool contrast agent is especially preferably a superparamagnetic iron oxide, e.g. as disclosed in WO97/25073, especially one coated with a starch residue and particularly one also coated with an opsonisation inhibitor such as for example PEG. The use of such contrast agents has been described by Røhl et al. Acta Radiologica 40: 282-290 (1999). These materials are especially suitable since they combine a strong T_2^* in a bolus phase with a predominant T_2 effect in the steady state. Furthermore, they remain in the vascular space during kidney transit, and they are not nephrotoxic and do not rely on renal excretion and so are particularly safe for use with patients with compromised renal function.

The MR imaging in the method of the invention preferably involves image acquisition at least two times, once during first passage of a bolus of the contrast agent through the kidney and a second after the contrast agent has become substantially uniformly distributed in the blood, e.g. after 1 to 30 minutes, preferably 3 to 15 minutes, following bolus administration of the contrast agent. Desirably the first image is T_1, T_2, or T_2^*-weighted and the second T_1-weighted. Especially preferably, image generation is also affected before contrast agent administration or before arrival of the contrast agent at the kidney, i.e.

a native or non-contrast enhanced image is preferably acquired.

Thus, in a preferred embodiment, the invention provides a method of MR imaging of the kidney in a vascularised human or non-human animal body, said method comprising administering into the vasculature of said body a bolus of a blood pool MR contrast agent (e.g. intravenous injection), preferably a superparamagnetic contrast agent, generating a contrast-enhanced MR image, preferably a T_1*-weighted image, of said kidney during the first pass of said contrast agent, and after the concentration of said contrast agent throughout the blood of said body has become substantially uniform generating at least one further MR image, preferably a T_1-weighted image, of said kidney, and optionally deriving from said MR images values indicative of renal perfusion and renal artery stenosis grade.

In the methods of the invention, the first pass T_1*-weighted image, which essentially provides perfusion information, can be superimposed upon the subsequent T_1-weighted image, which provides morphological information so as to permit the physician to view directly the correlation between a stenosis and a hypoperfused or non-perfused area within the kidney.

As mentioned earlier, renal hypertension or insufficiency may be caused by renal artery stenosis or by parenchymal damage. Evaluation and grading of renal artery stenosis is achievable using the methods of the present invention, in particular where the steady state images are generated from a volumetric (3D) image acquisition, enabling reconstruction in any plane and any projection within the acquired volume. Assessment of parenchymal damage can be performed according to the methods of the invention by using the first pass images to quantify intra-parenchymal blood volume. The quantitative data thus generated from the two sets of images may then be correlated with each other to enable

the physician to differentiate between renovascular and renoparenchymal damage and assess the likelihood of success for interventional surgery.

Viewed from a further aspect, the invention thus provides a method of differentiation between renovascular damage and renoparenchymal damage in a kidney in a vascularised human or non human body wherein a blood pool MR contrast agent is administered into the vasculature of said body, preferably as a bolus, and images of said kidney are generated using imaging sequences and timing to permit both visualisation and gradation of renal artery stenosis and quantification of renal perfusion, and wherein the physiological and morphological state of said kidney is assessed.

While many varieties of blood pool MR contrast agents may be used, e.g. macromolecular or polymeric (e.g. dendrimeric) agents, blood protein binding agents, liposomal contrast agents and superparamagnetic iron oxides, it is particularly desirable to use the degraded starch-coated superparamagnetic iron oxides of WO97/25073. These are especially suitable for four reasons. Firstly due to the large magnetization associated with superparamagnetic particles they have predominant T_2^* effects during the first pass of the bolus. Secondly, due to their low r_2/r_1 ratio, T_1 effects dominate when a steady state, i.e. when a uniform distribution within the blood pool, has been achieved. Thirdly, due to the size and surface of the particles they remain in the intravascular space during the time course of the MR examination being subject neither to glomalular filtration nor to secretion (their ultimate elimination from the intravascular space is via the reticuloendothelial system). Fourthly, they are not nephrotoxic and not renally excreted and thus are suitable for use with patients with compromised renal function.

Contrast enhanced MR angiography is preferably

effected using fast spoiled gradient echo sequences with short T_R and T_E values. A complete 3D data set with high spatial resolution can be obtained in this way because of the prolonged T_1 shortening effect and long vascular half life of the agent. To obtain MR angiograms sufficiently clear for diagnostic use, the T_E of the blood needs to be reduced significantly - shorter T_1 of the blood, shorter T_R and higher flip angle result in higher contrast between the blood vessel and the surrounding tissues which will have higher T_1 values.

Desirably the blood pool MR contrast agent is administered at dosages sufficient to achieve T_1 values in blood, at steady state, of less than 300 ms, more preferably less than 200 ms and still more preferably less than 100 ms. T_1-weighted 3D spoiled gradient echo imaging is then preferably performed with T_k values of 1.5 to 50 ms, more preferably 2 to 20 ms, T_f values of 0.5 to 15 ms, more preferably 0.7 to 5 ms, and flip angles of 5 to 90, more preferably 10 to 60. Optionally a magnetisation preparation prepulse may be applied in order to increase the contrast between blood and surrounding tissues. The inversion time T1 should preferably be between 5 and 700 ms, more preferably between 10 and 600 ms, even more preferably between 15 and 500 ms. Although image acquisition following the prepulse is preferably a gradient echo sequence, echo planar (EPI) or RARE type acquisition schemes may also be applied. Since the blood pool MR contrast agent remains in the vasculature for a prolonged period, multiple breathold MR angiograms can be obtained. Generally one will first obtain a large volume data set with low spatial resolution and subsequently (having identified the region of interest) obtain small volume data sets with a higher spatial resolution, e.g. about 1 mm^3. These may be used to grade renal artery stenosis, e.g. in steps of 20%. A grade of 0% means blood flow is unaffected, while a grade of 100% means blood flow is

totally blocked. 50% can mean 50% reduction in arterial cross sectional area or 50% reduction in blood flow rate (i.e. mL/sec); for present purposes diameter is preferred. One clinically relevant grading scheme grades stenoses as 0%, less than 50%, 50 to 80%, and above 80% (see for example Hany et al. Radiology 204: 357-362 (1997), Snidow et al. Radiology 198: 725-732 (1996), Steffens et al. JMRI 7: 617-622 (1997), Bakker et al. Radiology 207: 497-504 (1998) and Wilman et al. Radiology 205: 137-146 (1997)).

In the method of the invention grading may be effected by measuring the vessel diameter at the point of maximum narrowing and the diameter of the normal vessel distal to the stenosis. The % stenosis is then determined from these two numbers.

The images which are used to grade renal artery stenosis may be digitally post-processed to remove overlaying renal veins if these otherwise affect interpretation of the stenosis. This may be achieved by selecting a projection in the 3D data set where the artery is not obscured by the vein. A vessel tracking algorithm may also be employed to identify the arterial structures.

Quantification of renal perfusion relies on the blood pool MR contrast agent being confined to the intravascular space during the course of the MR examination. In the methods of the invention the T_2^* properties of the contrast agent may be utilised in first pass imaging following bolus administration. However the T_1 properties of the contrast agent in the steady state may additionally or alternatively be used. In the T_2^* model, the MR signal variation in the tissue during the first pass of the contrast agent can be analysed according to any established tracer kinetic technique, e.g. using the methods of Schreiber et al. J. Cereb. Blood Flow Metab. 18: 1143 (1998) and Stritzke et al. IEEE Trans. Med. Imag. 9: 11 (1990).

For determination of blood flow per gram of tissue, the blood volume is divided by the mean transit time of the bolus, e.g. as described by Schreiber et al. in J. Cereb. Blood Flow Metals 18: 1143-1156 (1998). The mean transit time may be determined as shown in Schreiber et al. J. Cereb. Blood Flow Metab. 18: 1143 (1998), Remmp et al. Radiology 193: 637 (1994) and Stritzke et al. IEEE Trans. Med. Imag. 9: 11 (1990).

For the kidney, the renal artery (which supplies more than 99% of the blood to the kidney) may be used as the input function. A dual slice T_1-weighted sequence is desirably used for determination of the signal curve in the input function and the tissue. One slice is positioned perpendicular to the renal artery and the other is positioned perpendicular to the long axis of the kidney. In this way a sufficient amount of renal cortex and medulla is contained within the second slice. The contrast media bolus should be as tight as possible in order to minimise the contribution of T_1 effects to the signal curve. T_E is selected to be long enough to ensure T_1 weighting but not so long that signal drops right down to base line. The temporal resolution should be selected to be high enough to avoid under-sampling of the signal curve. Image acquisition time is thus preferably 5 sec or less, more preferably 2 sec or less, particular 1 sec or less. With an image acquisition time of 2 sec, 5 to 7 data points can be obtained during bolus arrival in the renal artery. Sampling (i.e. image acquisition) should preferably continue until signal has returned to base line. Additionally, image acquisition should desirably be during free-breathing since breathold alters renal artery blood flow. Data points of images with substantial motion therefore may have to be corrected by post processing or removed from the signal curve. Using this approach absolute values of cortical perfusion can be obtained. The values obtained for non-stenosed kidneys of adult foxhounds ranged

between 4 and 5 mL/g/min which was in good agreement with invasively obtained and literature data.

Typically, such a T_1-weighted (i.e. T_1-weighted) imaging sequence may require flip angle values of 5 to 90°, more preferably 10 to 60°.

Alternatively or additionally, blood volume may be accomplished by T_1 mapping in the steady state. High resolution T_1-images of the kidney and aorta are obtained and the relative change in R_1 due to the agent in a large vessel is compared to the relative change in a given tissue. The fractional difference in R_1 in tissue versus vessel is then directly related to the blood volume of the tissue, e.g. using the method of Bauer et al. Magn. Reson. Med. 35: 43-55 (1996).

The methods of the invention may desirably also involve administration of pharmacological agents which affect blood flow, e.g. vasoconstructive or vasodilating agents or blood clot dissolving agents, e.g. angioplasty (e.g. PCTA) or placement of a stent. In this way the physician can monitor the success of attempts to remove a stenosis.

A key issue in the comprehensive assessment and differentiation of renal disease is the systematic correlation of changes in renal perfusion to the morphological degree of renal artery stenosis. Thus in the Examples below, different states were simulated under controlled conditions.

In the dog model described in Example 1, different degrees of renal artery stenosis were artificially created with an invasively implanted rubber clamp. For each degree of stenosis, high-resolution MR angiograms as well as perfusion measurements were performed. The absolute values for cortical perfusion were correlated to the percentage of renal artery stenosis. For acutely induced renal artery stenoses in an otherwise healthy kidney, cortical perfusion remained constant over a large array of degrees of stenosis. Only stenoses

greater than 95% caused a substantial drop in parenchymal perfusion. These results demonstrate the uniqueness of the methods of the invention in two ways. First, this comprehensive approach obtains data that does not correlate linearly to the degree of stenosis and therefore does not provide redundant but rather additional information. Second, since there is a rather abrupt change of parenchymal perfusion, the cut-off point of exceeding the autoregulative capacity can be determined. Therefore, the functional significance of a stenosis can be quantified.

In addition, the methods of the invention were evaluated in chronic disease states. In patients with different degrees of renal artery stenosis, bilateral perfusion measurements were performed and the absolute values of cortical perfusion were correlated to the morphologic degree of renal artery stenosis obtained in the MR angiograms. By combined analysis of the morphologic and functional MR data, the following different disease states could be identified and differentiated based on the quantitative data:

- Low perfusion states with coexisting normal low-grade stenosis. This combination is caused by underlying primary renoparenchymal damage.
- Normal perfusion states with low-grade, functionally non-significant stenoses.
- Low perfusion states caused by the long presence of high-grade functionally significant stenoses.

The methods of the invention will now be illustrated further by the following non-limiting Examples and the accompanying drawings, in which:

Figure 1a shows contrast-enhanced MR angiograms obtained for different degrees of arterial stenosis (open arrow) in the same dog (left: no stenosis, middle: moderate (70%) stenosis, right high-grade (90%) stenosis);

Figure 1b shows T_1* weighted perfusion images

corresponding to each image in Fig 1a during peak arrival of the contrast agent bolus;

Figure 2a shows a contrast-enhanced MR angiogram revealing low-grade (~50%) stenosis (open arrow);

Figure 2b shows T* weighted perfusion images at peak arrival of the contrast agent bolus, revealing decreased perfusion in the left kidney (Fig 2b.1) and normal cortical perfusion in the right kidney (Fig 2b.2);

Figure 3 shows signal-time curves for the left (Fig 3a) and right (Fig 3b) kidney, corresponding to the images of Fig 2b.1 and 2b.2 respectively, showing input functions obtained in the left and right renal artery (dotted lines) and the resulting response curve in the corresponding cortical tissue (solid lines).

Example 1

Systematic correlation of the morphologic degree of stenosis to the corresponding perfusion changes in dogs

This Example demonstrates the systematic correlation between morphologic degree of stenosis and corresponding functional in terms of perfusion using both dynamic first pass and steady state imaging.

In a foxhound dog (weight approximately 30 kg) different degrees of renal artery stenosis were created by a rubber clamp, which was implanted around the renal artery. Angiographic and perfusion data were obtained using,

- bolus application of 1.5 ml of a 30 mg Fe/ml suspension of a superparamagnetic iron oxide prepared according to the description of Example 12 of WO97/25073, administered into the jugular vein at 5 mL/second,

- dynamic T_1-weighted perfusion imaging during first pass of the bolus for quantification of cortical blood flow (see Fig. 1b of the accompanying drawings),
- high-resolution contrast-enhanced MR angiography in the steady state (see Fig. 1a),
- estimation of the cortical blood volume in the steady state.

The images were recorded on a Siemens Vision 1.5T MR imaging apparatus using the following sequences:

The following results were obtained:

- In the high-resolution contrast-enhanced MR angiograms with a voxel size of 0.7 x 1.0 x 0.7mm, the different degrees of stenosis can be accurately identified as shown here for a non-stenosed artery (0%), a moderate stenosis (70%) and a high-grade stenosis (90%).
- The T_2 weighted images obtained during first pass reveal specific findings for the different degrees of stenosis. In the non-stenosed (0%) vessel, a normal corticomedullar differentiation is found with massive signal loss in the cortex during peak arrival of the bolus. Only minor changes in the medulla are present as a result of overall much lower perfusion. Mean flow was calculated as 4.2 ± 1.1 ml per gram of cortical tissue per minute. For the moderate stenosis, no apparent changes in renal perfusion are visible. Cortical perfusion stays constant. This indicates that at least in the acute state the autoregulation of the kidney still is able to maintain adequate perfusion, therefore this stenosis reveals no functional significance. For the high-grade stenosis (90%), a substantial drop in cortical perfusion is found with loss of corticomedullar differentiation. Absolute cortical

perfusion drops down to 2.1 ± 0.6 ml/g/min. This indicates that the cut-off point of the autoregulative capacity has been exceeded for this degree of stenosis. The blood volume required for absolute quantification of the cortical blood flow can be also calculated in the steady state by means of T measurements in the renal parenchyma and the aorta. This can be done for example using a saturation recovery gradient echo sequence (c) with varying inversion times, but this strategy is not limited to this particular technique.

A T_1*-weighted FLASH sequence was used with the following sequence parameters : T_R=15 ms, T_E=6 ms, flip angle=12 deg, FOV=200x200 mm, slice thickness=5 mm, scan time =1.92 secs. One slice was used to track the bolus passage of the agent in renal parenchyma, whereas the second slice was positioned perpendicular to the renal artery to measure the arterial input function (AIF). Signal-time-curves were converted to concentration-time curves according to an exponential relationship (see Schreiber et al. and Remmp et al. (both supra)). The tissue curves were deconvoluted with the AIF using a method based on the AIF by orthogonal functions (see Schreiber et al. and Stritzke et al. (both supra)).

According to the principles of indicator dilution theory, the region blood volume (rBV), regional blood flow (rBF) and mean transit time (MTT) were calculated in RIO's (150 to 280 pixel each) lying in the renal cortex and the medulla (see Schreiber et al., Remmp et al. and Stritzke et al. (all supra)).

The morphologic degree of stenosis, defined as the

percent change in artery diameter, was determined in the steady state. An additional 4.5 ml of the 30 mg Fe/ml suspension of the superparamagnetic iron oxide prepared according to the description of Example 12 of WO97/25073 was injected prior to imaging so that the total dose was 4.0 mg Fe/kg. Images were obtained using T_1-weighted 3D FEE sequences.

Example 2

Differentiation of renovascular and renoparenchymal disease in human patients

The comprehensive approach demonstrated in Example 1 was applied to a human subject and this differentiation of renoparenchymal damage from renovascular disease could be made based on the combined analysis of the angiographic and perfusion data. The patient presented with hypertension resistant to therapy and rising creatinine. The contrast-enhanced MR angiography performed in the steady state revealed only a low-grade stenosis of about 50% in the distal left renal artery (see Figure 2(a)), which was confirmed by conventional X-ray digital subtraction angiography. However, the dynamic T_1 perfusion measurements demonstrated a dramatic decrease in cortical perfusion of the left kidney with loss of corticomedullar differentiation (see Figure 2(b.1)). Calculated mean cortical flow was only 1.8 ± 0.7 ml/g/ min (see Figure 3(a)). The normal right kidney revealed a cortical blood flow of about 4.2 ± 0.9 ml/g/min (see Figures 2(b.2) and 3(b)). The substantially smaller response of the left cortex can be seen by comparison of left (Fig 3a) and right (Fig 3b) response curves (solid lines). These findings were confirmed by Tc-99-MAG3-scintigraphy, which showed only 23% of the left kidney function remaining compared to

77% of the right kidney function. Based on these findings, the diagnosis of an underlying renoparenchymal damage could be established with coexistence of a non-functionally significant renal artery stenosis. Based on the comprehensive MR information the patient did not undergo surgery.

Claims

1. A method of magnetic resonance imaging of the kidney in a vascularised human or non human body wherein a blood pool MR contrast agent is administered into the vasculature of said body and images of said kidney are generated using imaging sequences and timing to permit both visualisation and gradation of renal artery stenosis and quantification of renal perfusion, and, optionally, values indicative of renal artery stenosis grade and renal perfusion are generated from said images or from detected magnetic resonance signals capable of transformation into said angiograms.

2. A method of differentiation between renovascular damage and renoparenchymal damage in a kidney in a vascularised human or non human body wherein a blood pool MR contrast agent is administered into the vasculature of said body and images of said kidney are generated using imaging sequences and timing to permit both visualisation and gradation of renal artery stenosis and quantification of renal perfusion, and wherein the physiological and morphological state of said kidney is assessed.

3. A method as claimed in claim 1 or claim 2 wherein said blood pool MR contrast agent is a superparamagnetic contrast agent.

4. A method as claimed in any of claims 1 to 3 wherein said blood pool MR contrast agent comprises magnetic iron oxide particles having on their surfaces an optionally modified polysaccharide and optionally a material which inhibits opsonization.

5. A method as claimed in any of claims 1 to 4 wherein said blood pool MR contrast agent comprises

superparamagnetic iron oxide particles having on their surfaces degraded starch and optionally a functionalised PEG.

6. A method as claimed in any of claims 1 to 5 wherein said blood pool MR contrast agent is administered as a bolus.

7. A method of claim 6 wherein a contrast enhanced image of said kidney is generated during the first pass of said contrast agent.

8. A method of claim 7 wherein said image is a T_2*-weighted image.

9. A method of any of claims 6 to 8 wherein at least one further image of said kidney is generated after the concentration of said contrast agent throughout the blood of said body has become substantially uniform.

10. A method of claim 9 wherein at least one T_1-weighted image is generated after the concentration of said contrast agent throughout the blood of said body has become substantially uniform.

11. A method of claim 9 or claim 10 comprising at least one further administration of said contrast agent.

12. A method of any of claims 1 to 11 wherein values indicative of renal perfusion and renal artery stenosis grade are derived from said MR images.

13. The use of a blood pool MR contrast agent for the manufacture of a contrast medium for use in a method of diagnosis comprising a method according to any of claims 1 to 12.

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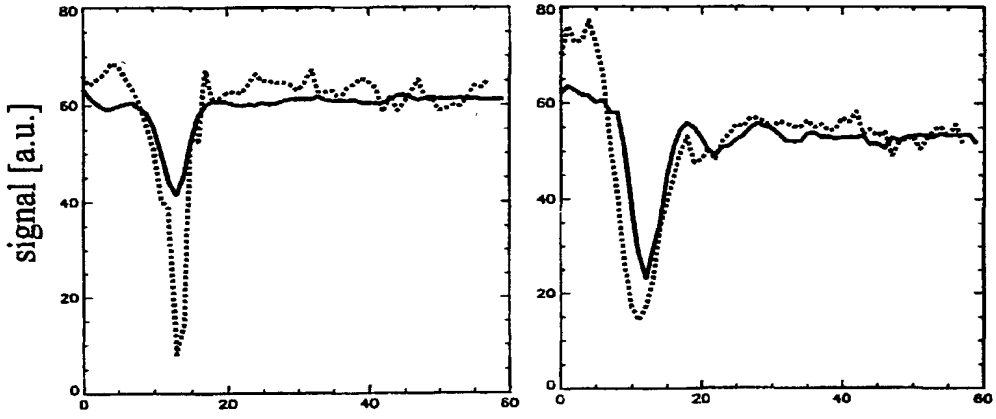
[Continued on next page]

(54) Title: METHOD OF MAGNETIC RESONANCE IMAGING



(57) Abstract: A method of magnetic resonance imaging of the kidney in a vascularised human or non human body wherein a blood pool MR contrast agent, preferably a paramagnetic contrast agent, is administered as a bolus into the vasculature of said body and images of said kidney are generated using imaging sequences and timing to permit both visualisation and gradation of renal artery stenosis and quantification of renal perfusion, and, optionally, values indicative of renal artery stenosis grade and renal perfusion are generated from said images. Preferably, T_2*-weighted images are generated during the first pass T_1-weighted images are generated. after the concentration of contrast agent throughout the blood has become substantially uniform.

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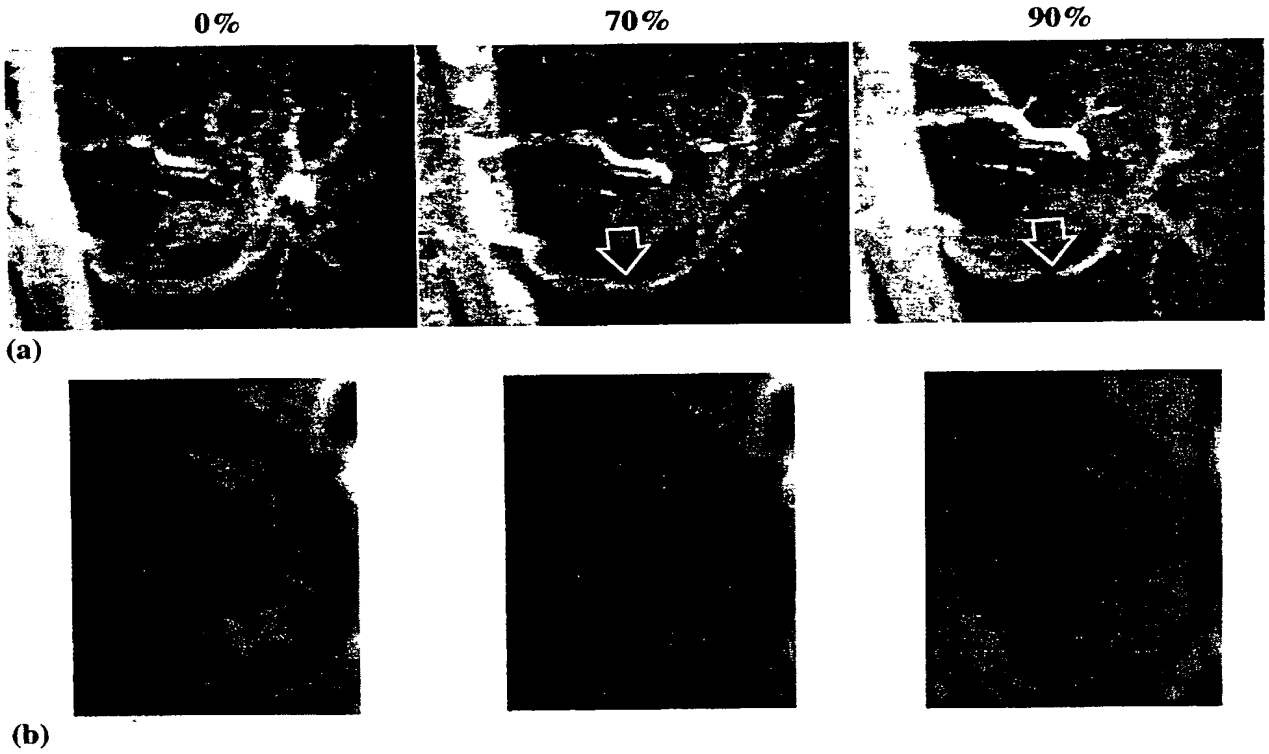


Fig 1

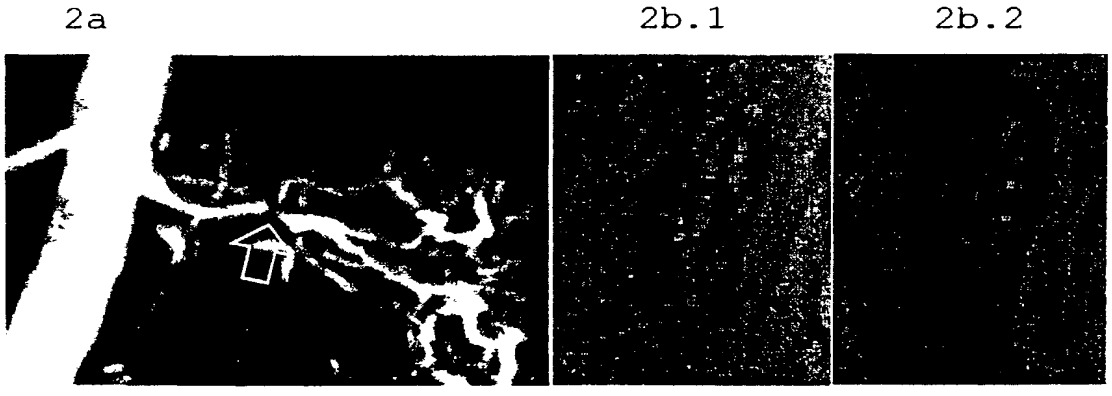


Fig 2

Fig 3a

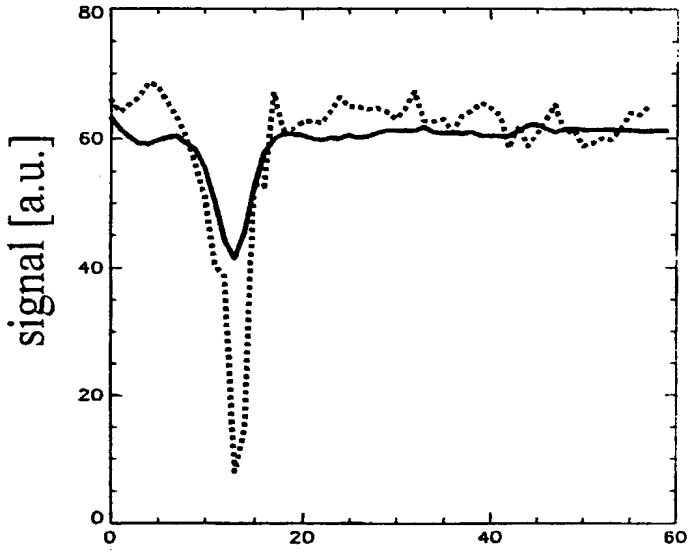
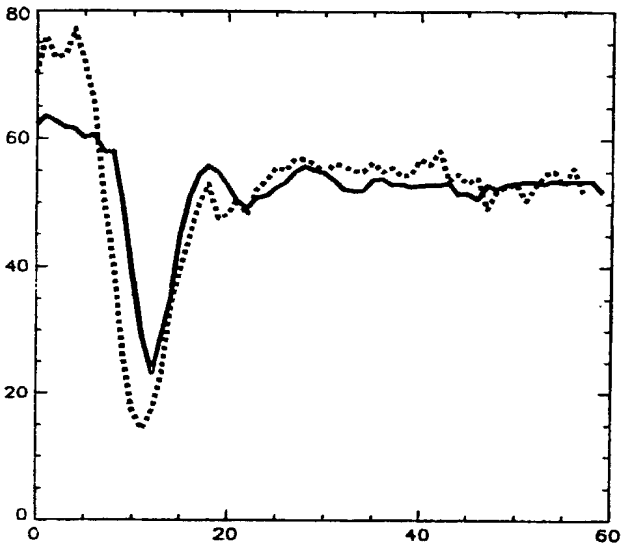


Fig 3b



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First Named Inventor	A. Bjornerud
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As a below named inventor, I hereby declare that:

My residence, post office address, and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled

Method of Magnetic Resonance Imaging

(Title of the Invention)

the specification of which
☐ is attached hereto
OR
☒ was filed on (MM/DD/YYYY) 05/22/2000 as United States Application Number or PCT International Application Number PCT/GB00/01960 and was amended on (MM/DD/YYYY) _____ (if applicable).

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment specifically referred to above.

I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR 1.56.

I hereby claim foreign priority benefits under 35 U.S.C. 119(a)-(d) or 365(b) of any foreign application(s) for patent or inventor's certificate, or 365(a) of any PCT international application which designated at least one country other than the United States of America, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate, or of any PCT international application having a filing date before that of the application on which priority is claimed

Prior Foreign Application Number(s)	Country	Foreign Filing Date (MM/DD/YYYY)	Priority Not Claimed	Certified Copy Attached? YES	NO
9911939.8	Great Britain	05/21/1999	☐	☐	☒
0007867.5	Great Britain	03/31/2000	☐	☐	☒
			☐	☐	☐
			☐	☐	☐

☐ Additional foreign application numbers are listed on a supplemental priority data sheet PTO/SB/02B attached hereto.

I hereby claim the benefit under 35 U.S C 119(e) of any United States provisional application(s) listed below

Application Number(s)	Filing Date (MM/DD/YYYY)

☐ Additional provisional application numbers are listed on a supplemental priority data sheet PTO/SB/02B attached hereto.

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Please type a plus sign (+) inside this box → [+]

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DECLARATION — Utility or Design Patent Application

I hereby claim the benefit under 35 U.S.C. 120 of any United States application(s), or 365(c) of any PCT international application designating the United States of America, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of 35 U S.C 112, I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR 1 56 which became available between the filing date of the prior application and the national or PCT international filing date of this application.

U.S. Parent Application or PCT Parent Number	Parent Filing Date (MM/DD/YYYY)	Parent Patent Number *(if applicable)*
PCT/GB00/01960	05/22/2000	

☐ Additional U.S. or PCT international application numbers are listed on a supplemental priority data sheet PTO/SB/02B attached hereto

As a named inventor, I hereby appoint the following registered practitioner(s) to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith ☒ Customer Number 22840 *OR* ☐ Registered practitioner(s) name/registration number listed below → *Place Customer Number Bar Code Label here*

Name	Registration Number	Name	Registration Number

☐ Additional registered practitioner(s) named on supplemental Registered Practitioner Information sheet PTO/SB/02C attached hereto.

Direct all correspondence to: ☒ Customer Number or Bar Code Label 22840 *OR* ☐ Correspondence address below

Name					
Address					
Address					
City		**State**		**ZIP**	
Country		**Telephone**		**Fax**	

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. 1001 and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Name of Sole or First Inventor: ☐ A petition has been filed for this unsigned inventor

Given Name (first and middle [if any])	Family Name or Surname
Atle	Bjornerud

Inventor's Signature						**Date**	
Residence: City		**State**		**Country**	NO	**Citizenship**	NO
Post Office Address	Nycomed Imaging AS, Nycoveien 1-2						
Post Office Address	N-0401 Oslo Norway						
City		**State**		**ZIP**		**Country**	

☒ Additional inventors are being named on the 2 supplemental Additional Inventor(s) sheet(s) PTO/SB/02A attached hereto

Please type a plus sign (+) inside this box → [+]

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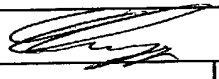
DECLARATION

ADDITIONAL INVENTOR(S)
Supplemental Sheet
Page 1 of 2

Name of Additional Joint Inventor, if any:	☐ A petition has been filed for this unsigned inventor						
Given Name (first and middle [if any])			Family Name or Surname				
Karen			Briley-Saebo				
Inventor's Signature						**Date**	
Residence: City		**State**		**Country**	NO	**Citizenship**	US
Post Office Address	Nycomed Imaging AS, Nycoveien 1-2						
Post Office Address	N-0401 Oslo Norway						
City		**State**		**ZIP**		**Country**	

Name of Additional Joint Inventor, if any:	☐ A petition has been filed for this unsigned inventor						
Given Name (first and middle [if any])			Family Name or Surname				
Michael V.			Knopp				
Inventor's Signature						**Date** 4/14/99	
Residence: City	SANDHAUSEN	**State**		**Country**	~~US~~ GERMANY	**Citizenship**	DE
Post Office Address	BERLINER STR. 7						
Post Office Address							
City	SANDHAUSEN	**State**		**ZIP**	69207	**Country**	GERMANY

Name of Additional Joint Inventor, if any:	☐ A petition has been filed for this unsigned inventor						
Given Name (first and middle [if any])			Family Name or Surname				
Stephen			McGill				
Inventor's Signature						**Date**	
Residence: City		**State**		**Country**	NO	**Citizenship**	GB
Post Office Address	Parkveien 6B						
Post Office Address	N-0350 Oslo Norway						
City		**State**		**ZIP**		**Country**	

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DECLARATION

ADDITIONAL INVENTOR(S)
Supplemental Sheet
Page 2 of 2

Name of Additional Joint Inventor, if any:				☐ A petition has been filed for this unsigned inventor			
Given Name (first and middle [if any])				Family Name or Surname			
Stefan O.				Schoenberg			
Inventor's Signature						**Date**	
Residence: City		**State**		**Country**	DE	**Citizenship**	DE
Post Office Address	Groshadern Klinikum, Inst. fur klinische Radiologie, Marchioninistr. 15						
Post Office Address	81377 Munchen Germany						
City		**State**		**ZIP**		**Country**	

Name of Additional Joint Inventor, if any:				☐ A petition has been filed for this unsigned inventor			
Given Name (first and middle [if any])				Family Name or Surname			
Inventor's Signature						**Date**	
Residence: City		**State**		**Country**		**Citizenship**	
Post Office Address							
Post Office Address							
City		**State**		**ZIP**		**Country**	

Name of Additional Joint Inventor, if any:				☐ A petition has been filed for this unsigned inventor			
Given Name (first and middle [if any])				Family Name or Surname			
Inventor's Signature						**Date**	
Residence: City		**State**		**Country**		**Citizenship**	
Post Office Address							
Post Office Address							
City		**State**		**ZIP**		**Country**	

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DECLARATION FOR UTILITY OR DESIGN PATENT APPLICATION (37 CFR 1.63)

☐ Declaration Submitted with Initial Filing OR ☒ Declaration Submitted after Initial Filing (surcharge (37 CFR 1 16 (e)) required)

Attorney Docket Number	NIDN-10403
First Named Inventor	A. Bjornerud
COMPLETE IF KNOWN	
Application Number	10 /018,026
Filing Date	29-Oct-2001
Group Art Unit	To be assigned
Examiner Name	To be assigned

As a below named inventor, I hereby declare that:

My residence, post office address, and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled,

Method of Magnetic Resonance Imaging

(Title of the Invention)

the specification of which
☐ is attached hereto
OR
☒ was filed on (MM/DD/YYYY) 05/22/2000 as United States Application Number or PCT International Application Number PCT/GB00/01960 and was amended on (MM/DD/YYYY) _____ (if applicable).

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment specifically referred to above.

I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR 1.56

I hereby claim foreign priority benefits under 35 U S C. 119(a)-(d) or 365(b) of any foreign application(s) for patent or inventor's certificate, or 365(a) of any PCT international application which designated at least one country other than the United States of America, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate, or of any PCT international application having a filing date before that of the application on which priority is claimed.

Prior Foreign Application Number(s)	Country	Foreign Filing Date (MM/DD/YYYY)	Priority Not Claimed	Certified Copy Attached? YES	NO
9911939.8	Great Britain	05/21/1999	☐	☐	☒
0007867.5	Great Britain	03/31/2000	☐	☐	☒
			☐	☐	☐
			☐	☐	☐

☐ Additional foreign application numbers are listed on a supplemental priority data sheet PTO/SB/02B attached hereto.

I hereby claim the benefit under 35 U S C. 119(e) of any United States provisional application(s) listed below

Application Number(s)	Filing Date (MM/DD/YYYY)	
		☐ Additional provisional application numbers are listed on a supplemental priority data sheet PTO/SB/02B attached hereto.

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U.S. Parent Application or PCT Parent Number	Parent Filing Date (MM/DD/YYYY)	Parent Patent Number (if applicable)
PCT/GB00/01960	05/22/2000	

☐ Additional U S or PCT international application numbers are listed on a supplemental priority data sheet PTO/SB/02B attached hereto

As a named inventor, I hereby appoint the following registered practitioner(s) to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith. ☒ Customer Number 22840 → *Place Customer Number Bar Code Label here*
OR
☐ Registered practitioner(s) name/registration number listed below

Name	Registration Number	Name	Registration Number

☐ Additional registered practitioner(s) named on supplemental Registered Practitioner Information sheet PTO/SB/02C attached hereto

Direct all correspondence to ☒ Customer Number or Bar Code Label 22840 *OR* ☐ Correspondence address below

Name					
Address					
Address					
City		State		ZIP	
Country		Telephone		Fax	

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true, and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U S C 1001 and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Name of Sole or First Inventor: ☐ A petition has been filed for this unsigned inventor

Given Name (first and middle [if any])	Family Name or Surname
Atle	Bjornerud

Inventor's Signature						Date	24/4/01
Residence: City		State		Country	NO	Citizenship	NO
Post Office Address	Olaf Bulls vei 46						
Post Office Address	N-0765 Oslo Norway NOY						
City		State		ZIP		Country	

☒ Additional inventors are being named on the 2 supplemental Additional Inventor(s) sheet(s) PTO/SB/02A attached hereto

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ADDITIONAL INVENTOR(S)
Supplemental Sheet
Page 1 of 2

Name of Additional Joint Inventor, if any:	☐ A petition has been filed for this unsigned inventor						
2.0 Given Name (first and middle [if any])	Karen			Family Name or Surname	Briley-Saebo		
Inventor's Signature	Kari Briley Saebo					Date	25/2/02
Residence: City		State		Country	NO	Citizenship	US
Post Office Address	Nycomed Imaging AS, Nycoveien 1-2						
Post Office Address	N-0401 Oslo Norway N/0 X						
City		State		ZIP		Country	

Name of Additional Joint Inventor, if any:	☐ A petition has been filed for this unsigned inventor						
3.0 Given Name (first and middle [if any])	Michael V.			Family Name or Surname	Knopp		
Inventor's Signature						Date	
Residence: City		State		Country	US	Citizenship	DE
Post Office Address	Ohio State University Hospital, Dept. of Radiology						
Post Office Address	171 Means Hall, 1654 Upham Drive						
City	Columbus	State	OH	ZIP	43210	Country	US

Name of Additional Joint Inventor, if any:	☐ A petition has been filed for this unsigned inventor						
4.0 Given Name (first and middle [if any])	Stephen			Family Name or Surname	McGill		
Inventor's Signature						Date	
Residence: City		State		Country	NO	Citizenship	GB
Post Office Address	Parkveien 6B						
Post Office Address	N-0350 Oslo Norway N/0						
City		State		ZIP		Country	

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ADDITIONAL INVENTOR(S)
Supplemental Sheet
Page 1 of 2

Name of Additional Joint Inventor, if any:	☐ A petition has been filed for this unsigned inventor
Given Name (first and middle [if any])	Family Name or Surname
Karen	Briley-Saebo

Inventor's Signature						Date	
Residence: City		State		Country	NO	Citizenship	US
Post Office Address	Nycomed Imaging AS, Nycoveien 1-2						
Post Office Address	N-0401 Oslo Norway						
City		State		ZIP		Country	

Name of Additional Joint Inventor, if any:	☐ A petition has been filed for this unsigned inventor
Given Name (first and middle [if any])	Family Name or Surname
Michael V.	Knopp

Inventor's Signature						Date	
Residence: City		State		Country	US	Citizenship	DE
Post Office Address	Ohio State University Hospital, Dept. of Radiology						
Post Office Address	171 Means Hall, 1654 Upham Drive						
City	Columbus	State	OH	ZIP	43210	Country	US

Name of Additional Joint Inventor, if any:	☐ A petition has been filed for this unsigned inventor
Given Name (first and middle [if any])	Family Name or Surname
Stephen	McGill

Inventor's Signature						Date	21 April 2002
Residence: City		State		Country	NO	Citizenship	GB
Post Office Address	149 Coloeherne Court, Redcliffe Gardens						
Post Office Address	London S.W.5 0DY, England						
City		State		ZIP		Country	

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DECLARATION

ADDITIONAL INVENTOR(S)
Supplemental Sheet
Page 2 of 2

Name of Additional Joint Inventor, if any:	☐ A petition has been filed for this unsigned inventor
Given Name (first and middle [if any])	Family Name or Surname
5-0 Stefan O.	Schoenberg
Inventor's Signature: Stefan O. Schoenberg	Date: 15/03/02
Residence: City	State	Country: DE	Citizenship: DE
Post Office Address: Bahnhofstrasse 28	
Post Office Address: 76870 Kandel, Germany DEX	
City	State	ZIP	Country

Name of Additional Joint Inventor, if any:	☐ A petition has been filed for this unsigned inventor
Given Name (first and middle [if any])	Family Name or Surname
Inventor's Signature	Date
Residence: City	State	Country	Citizenship
Post Office Address	
Post Office Address	
City	State	ZIP	Country

Name of Additional Joint Inventor, if any:	☐ A petition has been filed for this unsigned inventor
Given Name (first and middle [if any])	Family Name or Surname
Inventor's Signature	Date
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